PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	02.12.2005

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
C2949-PCT	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/BE2004/000118	16.08.2004	14.08.2003

Applicant
D. COLLEN RESEARCH FOUNDATION VZW et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference C2949-PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/BE2004/000118	International filing date *(day/month/year)* 16.08.2004	Priority date *(day/month/year)* 14.08.2003
International Patent Classification (IPC) or national classification and IPC A61P07/02, A61K39/395, C07K16/36		
Applicant D. COLLEN RESEARCH FOUNDATION VZW et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.03.2005	02.12.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Covone-van Hees, M.G Telephone No. +31 70 340-4416

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-75	as originally filed

Sequence listings part of the description, Pages

1-20	as originally filed

Claims, Numbers

1-33	received on 27.04.2005 with letter of 22.04.2005

Drawings, Sheets

1/14-14/14	as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 15-18 (as to IA) and 15 (partially)

because:

☒ the said international application, or the said claims Nos. 15-18 (as to IA) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 15 (partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-33
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-33
Industrial applicability (IA)	Yes:	Claims	1-14,20-33
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 **Rule 67.1(iv) PCT**

1.1 Claims 15-19 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

2 **Art. 5 and 6 PCT**

2.1 Claim 15 relates to an extremely large number of possible methods of treatments, without any indication of the addressed treatment. Support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found, however, for only a very small proportion of the methods claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search and examination over the whole of the claimed scope is impossible. Consequently, the search and examination has been carried out for those parts of the claim which appear to be supported and disclosed, namely those parts relating to the method for treatment comprising administering the antibody Krix-1 identified by seq.ID 1-4 (DNA and amino acid sequence of the heavy and light chain; see pg.13 and pg. 58 l.19-23 of the application), modified either by deglycosylation with N-glycosydase or by mutations at specific positions e.g. 49 (Thr to Ala) or at position 47 (Asn to Gln) (see ex. 7) produced in CHO cell line, to treat thromboembolic disorders (see ex.4-6,9).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: Wright A. et al. (1991)
D2: Kato M et al. (1993)
D3: Sato K et al. (1996)
D4: Khurana S et al. (1997)

D5: WO0104269 (cited by the applicant in the description)
D6: Singh I et al. (2002)
D7: Blood (2003)102(11):163a

1 **Article 19(2) PCT**

1.1 The amendments filed with the International Bureau under Art.19(1) PCT are in accordance with the requirements of Art.19(2) PCT.

2 **Article 6 PCT**

2.1 The applicant has amended the subject-matter of independent claim 1 by replacing the features "inhibitory antibody against FVIII" with reference to an antibody designed Krix-1, possibly in an attempt to restrict the scope of the claim to a specific antibody. The expression Krix-1 is, however, an internal designation for monoclonal antibodies, which in itself convey no technical information for the skilled person and is unclear in the sense of Art.6 PCT. In fact In order to clearly identify an antibody, amino acid and/or DNA sequence listing of both heavy and light chain **have to be included in the wording of the claim**. Alternatively, the antibody can be identified by means of the hybridoma deposit number producing it.

2.2 Consequently the subject-matter of amended claim 1 lacks support, essential technical features and clarity (Art. 6 PCT) the reason being the following:

2.3 D1 studies the effect of modifying the glycosylation of the variable region of an antibody binding to dextran (see abstract). This study clearly shows that changes in the position of the carbohydrate in the variable regions affect antigen binding in different ways, ranging from inhibitory to increased binding. Moreover the structure of the carbohydrate varied depending on the position in the variable region; and the amino acid substitution required to introduce the glycosylation consensus motif has also an impact on the affinity for the antigen (see pg.2717 right-hand column l.25-31; pg.2720 right-hand column l.1-6; pg.2721 left-hand column l.14-17; tab.II).

2.4 D2-D4 disclose specific monoclonal antibodies, glycosylated in the variable region, wherein modifying the glycosylation has completely different results. The antibody disclosed in D2 shows an improved binding to the specific antigen after deglycosylation (see abstract); whereas in D3, deglycosylation of the antibody has no impact on the binding properties (see abstract). But in D4, deglycosylation of the

antibody reduces the binding properties (see pg.467 left-hand column 2nd paragraph).

2.5 On the basis of D1-D4 it is obvious that modifications in the glycosylation of the variable region of antibodies have different effects which are strictly antibody dependent.

2.6 Therefore claim 1 is not supported by the description as required by Art.6 PCT, as its scope is broader than justified by the description and examples. The claim refers to "modified (Krix-1) antibodies", wherein "the glycosylation of its variable region has been modified resulting in a modified maximal inhibitory activity". However, the application exemplifies only the production of specific modified anti-Factor VIII monoclonal antibody (Krix-1 identified by seq.ID 1-4 (DNA and amino acid sequence of the heavy and light chain; see pg.13 and pg. 58 l.19-23 of the application), modified either by deglycosylation with N-glycosydase or by mutations at specific positions e.g. 49 (Thr to Ala) or at position 47 (Asn to Gln) (see ex. 7). In the light of the prior art (D1-D4) it appears unlikely that modification of a different inhibitory antibody would lead to the same result. The claim so lacks support over its whole broad scope.

2.7 Moreover, clear definition of the antibody is an essential technical feature to the definition of the invention. Since independent claim 1 does not contain al the essential features it does not meet the requirement following from Art.6 PCT taken in combination with Rule 6.3(b) PCT that any independent claim must contain all the technical features essential to the definition of the invention.

3 The same arguments cited for claim 1 point 2.1 are valid, mutatis mutandis, for those claims of the application, where an attempt to narrow the scope of the claim has been done by including reference to Krix-1 (claims 13,15,26).

4 The same objections cited for claim 1 points 2.2-2.7 are valid, mutatis mutandis, for claims 20 (and related product claim 24), 25 and 26 of the application.

5 **Novelty and Inventive Step** (Article 33(2) and (3) PCT)

5.1 The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claim 1 is novel (Art.33(2) PCT), but does not involve an inventive

step in the sense of Art. 33(3) PCT.

5.2 The above-mentioned lack of support, essential technical features and clarity notwithstanding, an attempt has been done to asses novelty and inventive step for the subject-matter of claim 1.

5.3 D5 is regarded as being the closest prior art to the subject-matter of present claim and discloses the production of an inhibitory anti-Factor VIII antibody Krix-1, characterised by heavy and light chains having 100% and >99% amino acid and DNA identity with the heavy and light chain of the antibody disclosed in the application (see ex.5 and fig.8 and 9). The applicant is the first to produce a Krix-1 antibody characterized in that the glycosylation of its variable region has been modified, resulting in a modified inhibitory activity. The subject-matter of claim 1 is therefore new in the light of the available prior art (Art.33(2) PCT).

5.4 In order to establish an inventive step, all the technical features necessary to solve the problem posed by the application should be present in the subject-matter of claim 1. In present case the applicant fails to indicate in the claim the specific modification of the variable region leading to modification in the inhibitory activity (see also point 2.6). Consequently, the way the claim is presently formulated does not show how to solve the problem of the application but is merely a reformulation of the problem itself and therefore does not meet the requirements of Art.33(3) PCT.

5.5 Dependent claims 2-12 do not contain any features which, in combination with the features of any claim to which they refer, would overcome the above mention objection and meet the requirements of the PCT in respect of inventive step.

6 The subject-matter encompassed by related products and methods claims 13-19 and 30-33 is new. An inventive step depends on the inventiveness of the product (according to claim 1), since said products and methods appear to be either standard products in this technical field (claim 13 and 14) or obvious methods in the light of the prior art. D6 shows the antithrombotic efficacy of LE2E9, an anti-factor VIII partially inhibitor antibody, in a mouse model for venous thrombosis (see the whole doc).

6.1 The subject-matter of claims 20 (and related product claim 24), 25 and 26 is new (Art.33(2) PCT), but not inventive (Art.33(3) PCT), the reasoning being the same, mutatis mutandis, as for claim 1.

6.2 Dependent claims 21-23,27-29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, since they do not appear to lead to any surprising effects or advantages.

7 For the assessment of the present claims 15-19 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

Certain published documents

Application No Patent No	Publication date *(day/month/year)*	Filing date *(day/month/year)*	Priority date *(valid claim)* *(day/month/year)*

Should the priority date of the present priority turn out not to be valid, then document "Blood (2003)102(11):163a" would become relevant in the context of novelty and inventive step

Re Item VII
Certain defects in the international application

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D4 and D6 are not mentioned in the description, nor are these documents identified therein.

Re Item VIII
Certain observations on the international application

1 Claims 9 and 10-12 are not supported by the description as required by Art.6 PCT. Present claims recite " at least 80% sequence similarity" and "at least 70% sequence similarity" respectively. Support however can only be found for antibodies comprising the specific sequence with a mutation to remove the glycosylation consensus site (see also point 1.2.2). The scope of the claims is therefore broader than justified by the description and examples.

2 The term "fragment" and "derivative" throughout the set of claims are vague and unclear and leave the reader in doubt as to the meaning of the technical features to which it refers, thereby rendering the definition of the subject-matter of said claims unclear, Art.6 PCT.

3 The expressions Krix-1, Krix-1Q, Krix-1A, Krix-1D and Krix-1E used throughout the set of claims are internal designations for monoclonal antibodies which in themselves convey no technical information for the skilled person (see also point 4). Thus, these expressions are unclear in the sense of Art.6 PCT.

Amended claims of international application PCT/BE2004/000118 (clean copy)

1. An antibody or fragment thereof which is a modified Krix-1 antibody, characterized in that the glycosylation of its variable region has been modified resulting in a modified maximal inhibitory activity compared to the native Krix-1 antibody.

2. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by modulating the glycosylation of the conserved N-glycosylation consensus pattern in the variable region of the Krix-1 antibody.

3. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by modifying the amino acid sequence of the N-glycosylation consensus sequence in the variable region of said Krix-1 antibody.

4. The antibody or fragment thereof according to claim 1, wherein said modification of the glycosylation is obtained by the introduction of a glycosylation consensus sequence in the variable region of the Krix-1 antibody.

5. The antibody or fragment thereof according to any of claims 1 to 4 wherein the affinity of said antibody is lower than 1nM.

6. The antibody or fragment thereof according to claim 1, which is KRIX-1Q or KRIX-1A or an scFv fragment, Fab fragment or F(ab')2 fragment of the monoclonal antibody KRIX-1Q or KRIX-1A.

7. The antibody or fragment thereof according to claim 1, which is KRIX-1D or KRIX-1E or an scFv fragment, Fab fragment or F(ab')2 fragment of the monoclonal antibody KRIX-1D or KRIX-1E.

8. The antibody or fragment thereof according to claim 1, wherein the scFv fragment is represented by SEQ ID NO: 26.

9. The antibody or fragment thereof according to claim 1, comprising an immunoglobulin heavy chain comprising an amino acid sequence sequence having at least 80% sequence similarity to SEQ ID NO: 2 within the CDR regions.

10. The antibody or fragment thereof according to claim 1, comprising an immunoglobulin heavy chain comprising a sequence encoded by a nucleotide sequence having at least 70% sequence identity to SEQ ID No 1.

11. The antibody or fragment thereof according to claim 1, comprising an immunoglobulin light chain comprising an amino acid sequence having at least 70% sequence similarity to SEQ ID No 4.

12. The antibody or fragment thereof according to claim 1, comprising an immunoglobulin light chain comprising a sequence encoded by a nucleotide sequence having at least 70% sequence identity to SEQ ID No 3.

13. A mixture of two or more antibodies or antibody fragments selected from the group consisting of a native inhibitory Krix-1 antibody against FVIII and the modified Krix-1 antibodies according to any one of claims 1 to 12.

14. A pharmaceutical composition comprising the antibodies according to any of claims 1 to 12 or the mixture of claim 13.

15. A method of treatment comprising administering an effective dose of the Krix-1 antibody or fragment thereof modified in such a way as to modify or introduce a glycosylation site in the antigen binding site of the Krix-1 antibody in order to modify the inhibitory effect of the Krix-1 antibody on the interaction(s) of the ligand(s) recognized by the Krix-1 antibody with other proteins or reagents interacting with the said ligand.

16. A method for treatment and prevention of thromboembolic disorders including but not limited to the prevention of deep vein thrombosis and pulmonary embolism secondary to surgical intervention, immobilization or chronic hereditary or acquired thrombophilia, and treatment of deep vein thrombosis, pulmonary embolism, stroke, atrial fibrillation, non Q wave myocardial infarct, non ST elevated myocardial infarct, unstable angina, sepsis or SIRS, comprising administering an effective dose of a monoclonal antibody or fragment thereof according to any of claims 1 to 12 or the mixture of claim 13.

17. A method for treatment and prevention of thromboembolic disorders comprising administering an effective dose of a monoclonal antibody or fragment thereof, according to any one of claims 1 to 12, or the mixture according to claim 13 and administered concomitantly to drug(s) inhibiting platelet aggregation, such as aspirin.

18. A method for treatment of acute myocardial infarct comprising administering an effective dose of a monoclonal antibody or fragment thereof according to any one of claims 1 to 12, or the mixture according to claim 13, and administered concomitantly to drug(s) inhibiting platelet aggregation, such as abciximab (Rheopro^{R}) or antithrombolytic agents (including tissue plasminogen activator, staphylokinase or microplasmin).

19. The method according to any of claims 15 to 18, wherein said monoclonal antibody is an anticoagulant monoclonal antibody derived from Krix-1 and carrying a mutation in the N-glycosylation site of the antigen binding site.

20. A method for obtaining a library of at least two inhibitory antibodies against factor VIII with variable maximal inhibitory activity, said method comprising modifying the glycosylation in the variable region of said inhibitory antibody and selecting at least one antibody or fragment having a different maximal inhibitory activity.

21. The method of claim 20, which method comprises the step of modifying the glycosylation in the variable region of an inhibitory antibody against FVIII or a fragment thereof, and selecting those antibodies for which the affinity is not substantially affected.

22. The method according to claim 20 or 21, wherein said factor VIII inhibitory antibody is directed against the C1 domain of FVIII.

23. The method according to any one of claims 20 to 22, wherein said factor VIII inhibitory antibody is Krix-1.

24. A library of factor VIII inhibitory antibodies obtained by the method according to claim 20 to 23.

25. A method for producing an FVIII inhibitory antibody or fragment thereof said antibody or fragment inhibiting FVIII between 20 and 85 % at saturating concentrations comprising the steps of:
- providing an intact FVIII inhibitory antibody or fragment thereof and,
- modifying the glycosylation of said antibody or antibody fragment at the post-translational level or modifying the glycosylation of said antibody or antibody fragment by altering essential amino acids in the glycosylation consensus sequence of the variable region of said antibody

26. A method for the identification of an antibody which competes with an inhibitory FVIII antibody, which is a modified Krix-1 inhibitory antibody having a modified glycosylation pattern, comprising the steps of:
- contacting FVIII or a fragment of FVIII comprising the C1 domain with a first inhibitory antibody, which is a modified Krix-1 inhibitory antibody having a modified glycosylation pattern, and a candidate inhibitory antibody, and.
- assaying the capacity of said candidate antibody to compete with the binding of said modified Krix-1 inhibitory antibody to said FVIII or fragment of FVIII.

27. The method of claim 26 wherein said first inhibitory antibody is Krix-1A, Krix-1Q, Krix1D or Krix-1E.

28. The method according to claim 27 further comprising the step of determining the capacity of said second antibody to inhibit FVIII activity.

29. The method according to claim 27 further comprising the step of determining the presence of a partial inhibitory effect on FVIII activity of said second antibody when said second antibody is present at a molar excess.

30. A mixture comprising an antibody according to any one of claims 1 to 12 with another antibody which is an inhibitory antibody against FVIII.

31. The mixture of claim 30, wherein said other antibody is antibody is RHD5.

32. The mixture of claim 13, 30 or 31, wherein said antibodies are mixed together in an appropriate ratio to achieve a given maximal inhibition of FVIII activity, whatever the excess of the mixture of antibodies over FVIII.

33. A pharmaceutical composition comprising the mixture of any one of claims 30 to 32.